Hypoxia Inhibits Cavin-1 and Cavin-2 Expression and Downregulates Caveolae in Adipocytes

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Résumé en anglais	During obesity, an hypoxic state develops within the adipose tissue resulting in insulin resistance. In order to understand the underlying mechanism, we analyzed the involvement of caveolae, since they play crucial role in the activation of insulin receptors. In the present study, we demonstrate that in 3T3-L1 adipocytes, hypoxia induces the disappearance of caveolae, and inhibits the expression of Cavin-1 and Cavin-2, two proteins necessary for the formation of caveolae. In mice, hypoxia induced by the ligature of the spermatic artery results in the decrease of Cavin-1 and -2 expression in the epididymal adipose tissue. Downregulation of expression of Cavins in response to hypoxia is dependent upon HIF-1. Indeed, inhibition of HIF-1 restores expression of Cavins and caveolae formation. Expression of Cavins regulates insulin signaling, since silencing of Cavin-1 and Cavin-2 impairs insulin signaling pathway. In human, Cavin-1 and -2 are decreased in the subcutaneous adipose tissue of obese diabetic patients compared to lean subjects. Moreover, the expression of Cavin-2 correlates negatively with HOMA-IR and HbA1c level. In conclusion, we propose a new mechanism where hypoxia inhibits Cavin-1 and Cavin-2 expression resulting in the disappearance of caveolae. This leads to the inhibition of insulin signaling and the establishment of insulin resistance.
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